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Complement is crucial in the pathogenesis of ANCA-associated vasculitis

Cees G.M. Kallenberg[1] and Peter Heeringa[2]

Renal lesions in ANCA-associated vasculitis (AAV) show an absence or paucity of immune deposits. Therefore, complement was not considered a major pathogenic factor. Data from an animal model of AAV, however, suggest involvement of the alternative pathway of complement. The paper by Gou *et al.* demonstrates activation also of the alternative and final common pathways in patients with AAV. Thus, the complement system might be a target for treatment in human AAV.

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The ANCA-associated vasculitides (AAVs) are characterized by systemic vasculitis in combination with the presence of anti-neutrophil cytoplasmic antibodies (ANCA) directed to either proteinase 3 (PR3) or myeloperoxidase (MPO). They include granulomatosis with polyangiitis (GPA), microscopic polyangiitis and its renal-limited form, and Churg–Strauss syndrome. The frequent involvement of the kidney is histologically apparent as necrotizing crescentic glomerulonephritis. In contrast to other forms of glomerulonephritis, deposits of immunoglobulins and complement, as studied by direct immunofluorescence of renal biopsies, are absent or scanty. Therefore, glomerulonephritis is designated as pauci-immune in the AAVs, and complement was suggested not to play a major role in the immunopathogenesis of these conditions. Nevertheless, a detailed study by Haas and Eustace[1] on 126 renal biopsies of patients with necrotizing crescentic glomerulonephritis with positive ANCA serology or necrotizing arteritis in the absence of known ANCA results showed glomerular immune deposits by electron microscopy in 68 biopsies (54%). The majority of the latter biopsies stained for at least one immunoglobulin or complement factor, and nearly half of the biopsies negative by electron microscopy showed positive immunofluorescence findings, although immunofluorescent staining was relatively weak in almost all biopsies. Despite these findings, AAVs were not considered immune complex-mediated conditions, and ANCA-induced neutrophil activation was presented as the key factor in their immunopathogenesis.[2]

Data from an animal model of MPO-ANCA vasculitis, however, suggested a critical role for complement in the induction of necrotizing crescentic glomerulonephritis.[3] In this model, anti-MPO antibodies are induced in MPO-deficient mice and transferred into wild-type mice, resulting in crescentic glomerulonephritis. When the recipient mice were deficient in complement C5 or factor B of the alternative pathway of complement, no disease developed. However, recipient mice deficient in C4, a factor of the classical and mannose-binding lectin pathways of complement, developed glomerulonephritis to the same extent as wild-type mice. When mice were pretreated with a C5-inhibiting monoclonal antibody, the development of lesions could be prevented. Treatment starting one day after disease induction strongly attenuated glomerular crescent formation.[4] These experimental data suggest that the alternative pathway of complement is involved in the pathogenesis of ANCA-associated glomerulonephritis and that intervening in complement activation can prevent disease progression.

IS COMPLEMENT INVOLVED IN HUMAN AAV?

As mentioned, the AAVs are designated as pauci-immune conditions, somewhat suggesting that immunoglobulins and complement are not directly involved in immunopathogenesis. Preliminary data from China, however, showed that factor B and properdin, components of the alternative pathway of complement, could be detected in glomeruli and small vessels of seven patients with pauci-immune AAV.[5] These factors colocalized with C3d and the membrane attack complex, suggesting that activation of the alternative pathway leads to renal damage. In contrast, C4d and mannose-binding lectin were not detected, indicating that both the classical pathway and the mannose-binding lectin pathway are not involved and excluding AAV as an immune complex-mediated disease. A second study by the same group on 12 patients with ANCA-negative pauci-immune crescentic glomerulonephritis, however, did detect C4d in eight and mannose-binding lectin in six renal biopsies.[6] In this issue of *Kidney International*, the same group of authors has, for the first time, analyzed plasma levels of complement components in 66 patients with active AAV and 54 with AAV in remission.[7] The findings are consistent with systemic activation of the alternative pathway of complement as demonstrated by increased levels of factor Bb

[1]*Department of Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands and* [2]*Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*

Correspondence: *Cees G.M. Kallenberg, Department of Rheumatology and Clinical Immunology, AA21 University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands. E-mail: c.g.m.kallenberg@umcg.nl*

and C3a following activation and decreased levels of properdin, possibly due to consumption. Furthermore, the final common pathway was activated, as reflected by increased levels of C5a and C5b-9, suggesting that complement activation is involved in the immune effector phase of AAV. This is also suggested by a decrease of activation factors during remission and the correlation of plasma levels of factor Bb during active disease with a score for clinical disease activity (Birmingham Vasculitis Activity Score) and with the proportion of (cellular) crescents in the renal biopsy. Somewhat surprisingly, the authors found increased levels of C4d in patients with active AAV, which did not decrease during remission. They speculate that the strong inflammatory process in AAV leads to accumulation of apoptotic and necrotic cells with increased production of C4d during their clearance. This, however, does not explain increased levels of C4d during remission. Otherwise, the absence of decreased levels of C2 and C4 during active disease (these levels were even increased) argues against consumption of C2 and C4 during activation of the classical and/or lectin pathway of complement activation. These data, being strongly supportive for a major role of complement in AAV, should be confirmed by others.

What are the clinical consequences of complement activation in AAV? As shown in their paper, Gou *et al.*[7] observed in particular a strong increase in plasma levels of C5a during active AAV. The anaphylatoxin C5a has a strong proinflammatory activity. In relation to ANCA-induced neutrophil activation, C5a is able to prime neutrophils, resulting, among others, in the expression of proteinase 3 (PR3) on the neutrophil membrane. Priming is a prerequisite for ANCA-induced neutrophil activation, allowing PR3-ANCA to interact with PR3 on the surface of the neutrophil. The signaling pathways involved in C5a priming have been defined, and blocking of these pathways with inhibitors of p38 MAPK, ERK, and PI3K decreases C5a-induced membrane expression of PR3 and release of lactoferrin from neutrophils activated by PR3-ANCA following C5a priming.[8] The interaction between C5a and its receptor on neutrophils has, indeed, been shown to cause a significant amplification loop for ANCA-induced neutrophil activation.[9] These observations are consistent with a recent study by Camous and colleagues demonstrating that neutrophils, stimulated by cytokines or coagulation factors, are able to activate the alternative complement pathway on their membrane, leading to the release of C5a fragments and further amplification of the inflammatory response.[10] Furthermore, the C5a receptor appeared to be essential for development of MPO-ANCA crescentic glomerulonephritis in an animal model.[9] The supposed role of C5a and its receptor in AAV is represented in Figure 1.

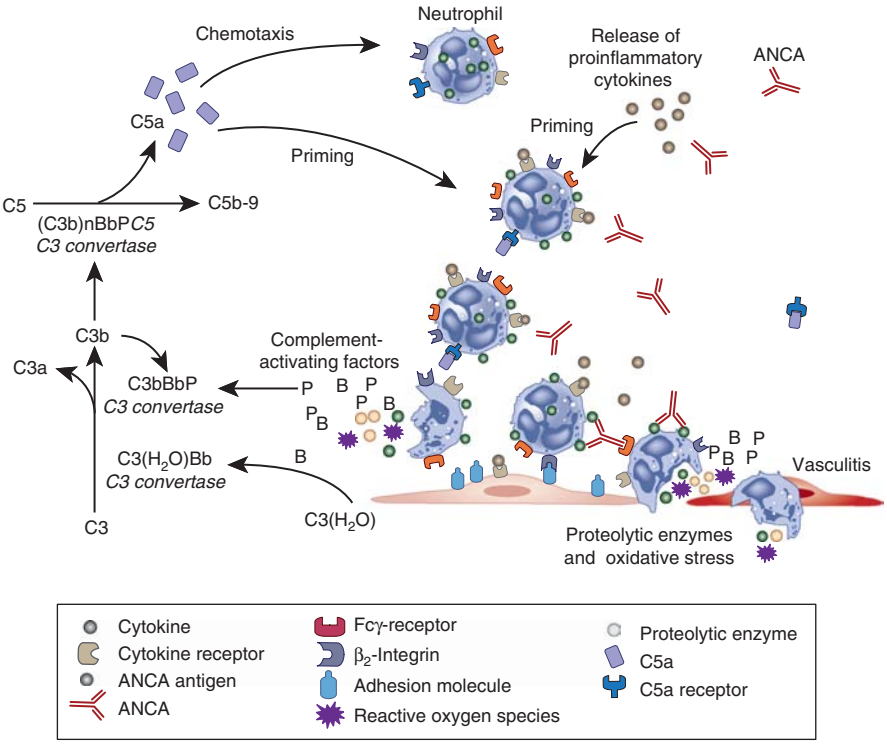

Figure 1 | Activation and effector mechanisms of complement in MPO-ANCA-mediated vasculitis. ANCA-mediated activation of cytokine-primed neutrophils causes production of reactive oxygen species and release of proteolytic enzymes, resulting in endothelial damage. Activation of neutrophils also induces the release of properdin (P) and factor B (B), both crucial for alternative pathway complement activation. Complement system activation leads to the generation of C5a, which amplifies the inflammatory response via enhanced neutrophil recruitment and priming of neutrophils for ANCA-mediated activation. (Adapted from: Van Timmeren MM, Heeringa P. Pathogenesis of ANCA-associated vasculitis: recent insights from animal models. *Curr Opin Rheumatol* 2012; 24: 8–14.)

It therefore seems logical to intervene in the C5a–C5a receptor interaction in patients with AAV. Indeed, a clinical trial evaluating the safety and efficacy of an inhibitor of the C5a receptor (CCX168), a small molecule that is orally administered, has been started in patients with ANCA-associated renal vasculitis (ClinicalTrials.gov identifier NCT01363388). The results of this trial, which are eagerly awaited, should demonstrate whether intervention in the complement system will become an essential step in the early treatment of patients with life-threatening AAV.

DISCLOSURE
The authors declared no competing interests.

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Access to kidney transplantation in Australia: does equal mean equitable?

Fergus J. Caskey[1] and Rommel Ravanan[1]

Sociodemographic gradients have been widely reported in end-stage renal disease treatment, as in the general population. So should we be relieved by the report from Grace *et al.* of no such gradient in access to deceased donor kidney transplantation in Australia? Although the authors have adjusted for the 'competing risk' of living kidney donor transplantation, which is higher in higher socioeconomic groups, it feels a little early to be reassured.

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Kidney transplantation offers patients with end-stage renal disease the greatest survival and quality-of-life opportunities, with the best results observed in those receiving kidneys from living donors.

In order for a patient to receive a kidney transplant, a number of steps must be successfully completed (Figure 1).[1] First, the potential recipient must receive accurate, balanced information about the treatment options available. Although this sounds straightforward, it relies on the treating clinician having the communication skills to raise the topic in a timely manner, provide appropriate information about the various treatment options, and identify potential barriers to transplantation for that individual. None of this can happen until the patient has been referred to a nephrologist and, in some settings, until he or she have been referred by that nephrologist to a transplant physician or surgeon. The various components of the transplant assessment need to be completed, each of which introduces delays as well as direct and indirect costs to the recipient. Although many national organizations have guidelines on suitability for kidney transplantation, these are largely based on expert opinion, and the final decision remains highly subjective. Once the patient is on the waiting list, organ allocation protocols largely take over.

Living kidney donor (LKD) transplantation introduces further potential barriers, costs, and delays. Balanced, informed information about the risks and benefits of all options needs to reach potential donors, who have to be healthy enough to donate and financially secure enough not to be dissuaded by the threat to their income, job, or future health-care costs.

It is in this context that we read the interesting report from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) on access to kidney transplantation in Australia (Grace *et al.*,[2] this issue). Studying all patients commencing renal replacement therapy in Australia from 2000 to 2010 ($n = 21{,}190$), Grace *et al.* report 93% higher preemptive transplantation rates for people living in the most affluent areas. All preemptive transplants were the result of LKD transplantation, and this higher rate of LKD transplantation persisted on to renal replacement therapy, with those from affluent areas having a 34% increased chance of receiving an LKD transplant

[1]*Richard Bright Renal Unit, Southmead Hospital, Bristol, UK*
Correspondence: *Fergus J. Caskey, Richard Bright Renal Unit, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, UK. E-mail: mdfjc@bris.ac.uk*